REMARKS

Upon entry of the amendments herein, claims 2-9 remain pending in the application. Claims 2 and 4 have been further amended herein. No new matter has been introduced by any of these amendments.

The Examiner has resurrected the rejection of claim 2 as indefinite because of the recitation of "a source of. . ." a number of times in step (1). In their August 13, 2001 Amendment and Response (pages 9-11), Applicants set forth cogent arguments against this ground of rejection. However, the Examiner made no comment on these arguments in her subsequent response, merely stating that the rejection was maintained for reasons of record. This notwithstanding, in the interest of expediting prosecution of the application, Applicants have amended the claim by deletion of the phrase in question in all instances.

The Examiner has also rejected claim 2 on the grounds that certain language in steps (3) and (4) is indefinite.

In the first place, it should be noted that the language which the Examiner contends is indefinite was orally agreed upon by the Examiner and Applicants' agent and was introduced in the wake of the Examiner's previous contention (See Paper No. 13, page 3) that "'radiolabelled peptidoglycan' [in step (3) of claim 2] lacks clear antecedent support in step 1) because in step 1), the 'UDP-N-acetyl glucosamine' is radiolabelled."

Furthermore, the recitation in step 3) of "peptidoglycan synthesized in steps 1)-2)," the Examiner's suggestion, would not be correct, since step 2) is clearly labeled as a step terminating synthesis. In any event, again in the interest of expediting prosecution, the steps have been amended to address the points made by the Examiner. Furthermore, Applicants have amended claim 4 in conjunction with the amending of step (1) of claim 2 in order to anticipate a possible objection by the Examiner to the same "source of" language found therein.

In light of the arguments set forth in Applicants' December 9, 2002 Amendment and Response, the Examiner has withdrawn the previous rejection of claims as being obvious over the combined teachings of the Elhammer, Mengin-Lecreulx and Kohlrausch references. However, the Examiner has leveled two new prior art rejections, the first one being of claims 2, 4, 5, 8 and 9 and again citing the Mengin-Lecreulx and Elhammer references, this time further in combination with the newly cited reference of US 6,428,971 to Shinabarger et al.

In withdrawing the previous prior art rejection, the Examiner has acknowledged that the combined teachings of the three then-cited references do not render obvious the instant invention. In leveling the first new rejection, the Examiner has cited the Elhammer and Mengin-Lecreulx references for essentially the same reasons as set forth before and has

replaced the Kohlrausch reference with Shinabarger. The Examiner apparently feels that the Shinabarger disclosure makes up for the deficiencies of the combined teachings of Elhammer and Mengin-Lecreulx, deficiencies that could not be remedied by the Kohlrausch disclosure. However, the Shinabarger disclosure is no more effective in the present determination of patentability than Kohlrausch.

It should be reemphasized that the Examiner has provided no new reasons for citing Elhammer and Mengin-Lecreulx; the same teachings, found inadequate in the wake of Applicants' last arguments, have been cited in the new rejection. The Examiner has found no additional teaching in these references to bolster the assertion of unpatentability.

Although the Examiner has acknowledged the inadequacy of the Elhammer and Mengin-Lecreulx references and, as set forth below, the newly cited Shinabarger reference cannot make up for this inadequacy, Applicants wish to reemphasize several points with respect to the Elhammer and Mengin-Lecreulx references.

First of all, it must be repeated that the instant invention is directed to an improved assay for the detection of peptidoglycan synthesis. The invention, clearly defined in claim 2, is a simple assay with advantages over a prior art paper chromatography method. The Examiner's attention is drawn to the section entitled "**[iv] Assay of *N*-acetylglucosaminyl**

transferase" in the first column on page 4628 of Mengin-Lecreulx. This is what constitutes the closest teaching to the instant invention in the cited prior art. It should be noted that this assay involves incubation of membranes with UDP-MurNac-pentapeptide before addition of the radiolabelled substrate. Reaction mixtures were then analyzed by paper chromatography. By contrast, the instantly claimed method does not employ time-consuming, inefficient paper chromatography. Rather, as set forth in claim 2, it involves step (2) to terminate peptidoglycan biosynthesis and steps (3) and (4) for solution-phase detection of peptidoglycan biosynthesis.

With respect to the Elhammer reference, Applicants do not argue that one of ordinary skill in the art looking to improve on the method of Mengin-Lecreulx might have been aware of Elhammer. However, such an artisan would have been aware that Elhammer's SPA assay relates to a specific eukaryotic enzyme and would have been particularly mindful of the Elhammer teaching on page 3, lines 9-15 that cloned enzymes are preferred, since membrane-bound enzymes complicate purification and *in vitro* uses of the enzyme.

Thus, there would have been no motivation to combine the teachings of Mengin-Lecreulx and Elhammer; in fact, if anything, the artisan would have been dissuaded from making such a

combination. This is the case irrespective of whether or not Elhammer teaches addition of divalent metal ion chelators.

With respect to the newly cited Shinabarger reference, Applicants do not deny that Shinabarger discloses an SPA utilizing lectin-treated beads. However, one of skill in the art reading Shinabarger would also have been aware that Shinabarger relates to a different specific enzyme, i.e., teichoic acid polymerase (TAP). This enzyme is not involved in peptidoglycan biosynthesis; the cell-wall teichoic acid pathway is distinct. The teaching of Shinabarger, et al. is that lipoteichoic acid can be used as a substrate for an important biological reaction that had previously had no substrate available for evaluating this reaction. The skilled artisan could not have tied this in with the other cited disclosure to arrive at the instant invention. In any event, even if the Shinabarger disclosure were more on target, and irrespective of whether or not Shinabarger teaches an SPA with lectin-coated beads, there would have been no motivation to combine Mengin-Lecreulx and Elhammer in the first place. Thus, whether or not Shinabarger discloses some deficiency in the other two references is irrelevant to the consideration of patentability.

The same lack of motivation to combine Mengin-Lecreulx and Elhammer in the first place also applies to the second new prior art rejection, that of claims 3, 6 and 7 as being obvious over

said references further in view of Shinabarger and Kohlrausch. Whether or not Kohlrausch teaches enzyme antagonists, and/or the pentapeptide precursor recited in instant claim 3, is insignificant in the present analysis, and this rejection should be withdrawn as well.

The technical reality of the state of the art in relation to assays for peptidoglycan biosynthesis immediately prior to the instant invention is best illustrated by the disclosure of Men, et al. previously made of record. This article was published only a few months before the earliest claimed priority date of the present application. It is important to reiterate some of the germane disclosure of Men, et al.:

> Although remarkable progress has been made in characterizing some of the early enzymes in the biosynthetic pathway, the downstream enzymes have proven exceedingly difficult to study. This is partly because the downstream enzymes are membrane-associated, making them intrinsically hard to handle, and partly because substrates for many of the enzymes are not readily available. These problems have impeded the development of active assays suitable for detailed mechanistic investigations of the downstream enzymes.

The article of Men et al. illustrates the recognition in the art of the difficulty of assaying downstream enzymes, such as those in the present invention, and illustrates that devising simple and direct assays for Mur G activity is not

straightforward. The article goes on to describe the use of a modified synthetic subtrate for Mur G. Thus, it is clear that the prior art failed to solve or practically suggest a solution to the technical problem to which the instant application is directed, i.e., the provision of a simple solution-phase assay for the detection of peptidoglycan biosynthesis.

The only way that the prior art can be said to lead to the instant invention is by the use of impermissible hindsight aided by the ignoring of dissuading teachings, particularly those of Elhammer and Men. In summary, the combination of Mengin-Lecreulx and Elhammer does not even meet the obvious-to-try standard, let alone the obvious-to-do standard, which latter standard is the one that the courts have deemed proper to apply.

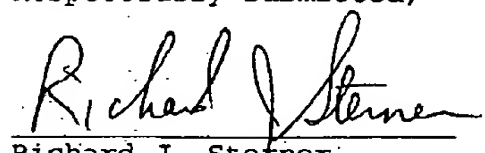
Accompanying this response is an Information Disclosure Statement by which two new references are made of record in the application.

In view of the amendments made herein to claim 2 and the arguments set forth above, the instant invention is claimed with definiteness and said invention is free of the prior art. Allowance of the application with pending claims 2-9 is respectfully requested. Should any other matters require attention prior to allowance, it is requested that the Examiner contact the undersigned.

The Commissioner is hereby authorized to charge any fees which may be due for any reason to Deposit Account No. 23-1703.

Dated: September 24, 2003

Respectfully submitted,



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